

# *Introduction to Post-marketing Drug Safety Surveillance: Pharmacovigilance in FDA/CDER*

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Center of Drug Evaluation and Research

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# Objectives

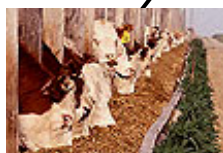
- Define Pharmacovigilance
- Describe the Division of Pharmacovigilance's (DPV's) key safety roles in FDA's Center for Drug Evaluation and Research (CDER).
- Understand components of postmarketing drug safety surveillance.
- Understand regulatory requirements and the role of MedWatch for reporting postmarketing safety information.
- Describe how adverse event reports are collected and analyzed by FDA/CDER/DPV

# Outline

- Pharmacovigilance Background
- Postmarketing Surveillance
- Spontaneous Adverse Event Reports and the FDA Adverse Event Reporting System (FAERS)
- Signal Detection
- Case Series Development and Evaluation
- Components of a Good Case Report



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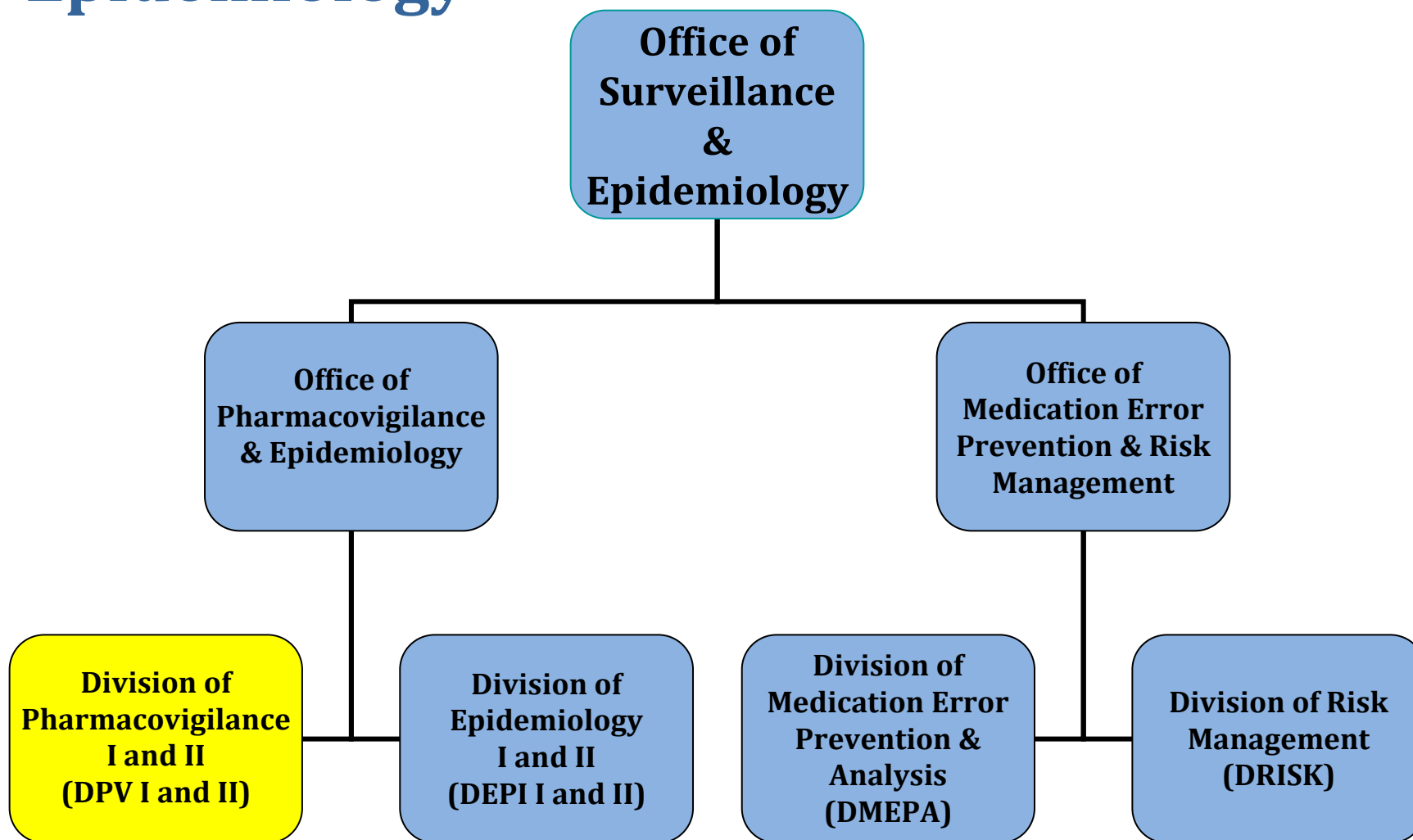


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# Pharmacovigilance

The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems.



\*The Importance of Pharmacovigilance, World Health Organization 2002

# Divisions of Pharmacovigilance

- Evaluate the safety of drug and therapeutic biologic products
- Advance public health by detecting and analyzing safety signals from all available data sources, utilizing evidence-based methods
- Recommend appropriate regulatory actions, including labeling changes, Risk Evaluation and Mitigation Strategies (REMS), etc.
- Communicate relevant safety information



# Safety Evaluators (SEs)

- 10 teams of SEs
  - Majority clinical pharmacists
  - Provide critical analysis of sources of postmarketing data to identify and evaluate safety signals
- Team coverage aligned with the Office of New Drugs (OND) review divisions' therapeutic areas
  - ~ 4-7 SEs per team (including Team Leader)
  - Each SE covers assigned product group(s) aligned with therapeutic area

# Medical Officers (MOs)

- Currently 11 MOs
- Provide clinical expertise in various therapeutic areas such as dermatology, infectious disease, rheumatology, pediatrics, etc.
- Collaborate with DPV teams on safety evaluation
- Collaborate with Office of New Drugs (OND) on safety evaluation

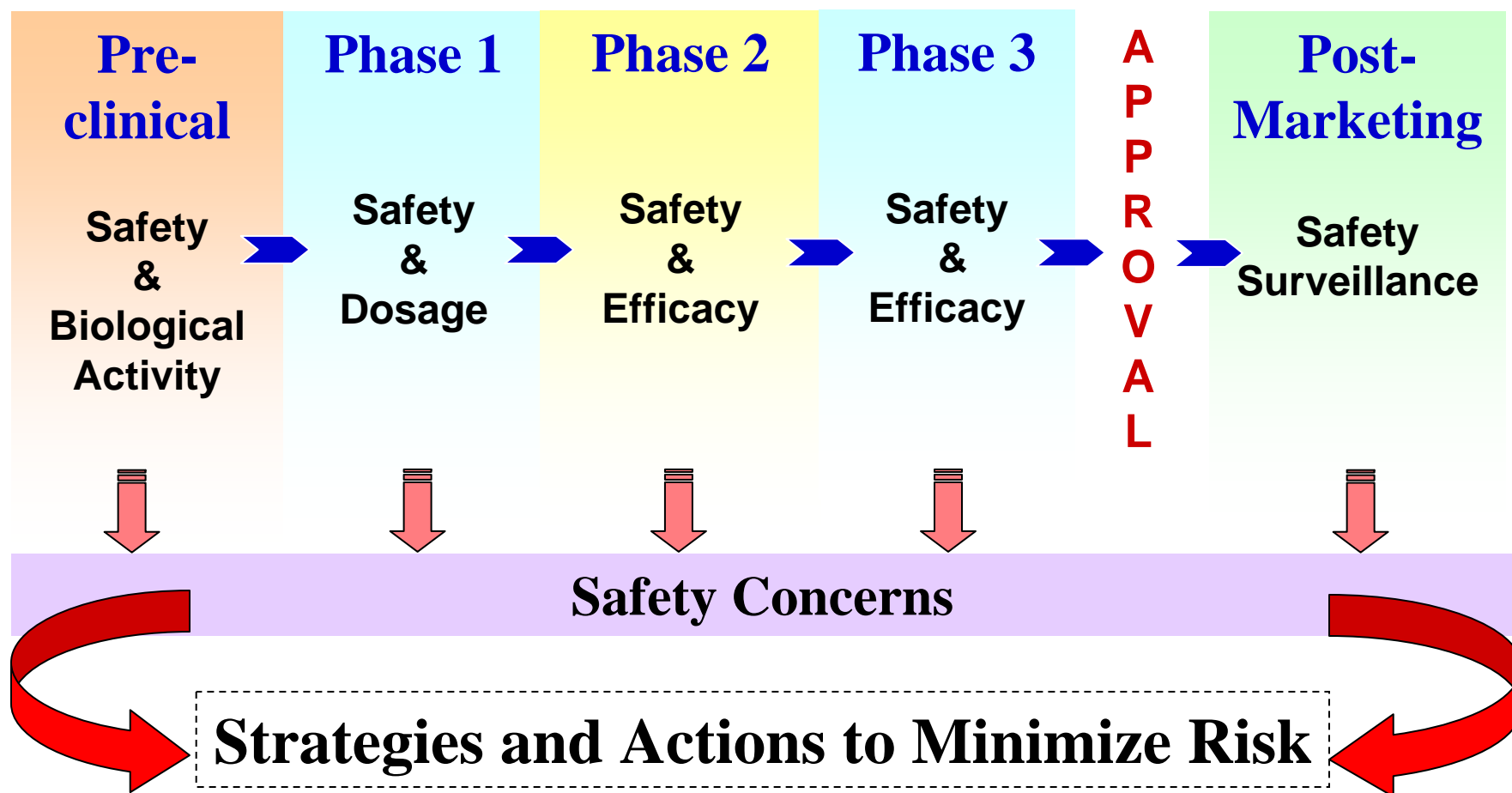
# Postmarketing Surveillance

# Challenge Question #1

## True or False

Safety data is only collected during the later phases of the clinical development program for a medical product.

# Safety in the Lifecycle of FDA-regulated Products



# Limitations of Premarketing Clinical Trials

- Size of the patient population studied
- Narrow population - often not providing sufficient data on special groups
- Narrow indications studied
- Short duration

# Benefits of Postmarketing Monitoring

The ability to study the following:

- Low frequency reactions (not identified in clinical trials)
- High risk groups
- Long-term effects
- Drug-drug/food interactions
- Increased severity and / or reporting frequency of known reactions

# Types of Postmarketing Surveillance

- Spontaneous/voluntary reporting of cases
  - National (FDA MedWatch)
  - Local or Regional (Joint Commission Requirement)
  - Scientific literature publications
- Postmarketing studies (voluntary or required)
  - Observational studies (including automated healthcare databases)
  - Randomized clinical trials
- Active surveillance
  - Drug-Induced Liver Injury Network (DILIN)
  - Sentinel initiative

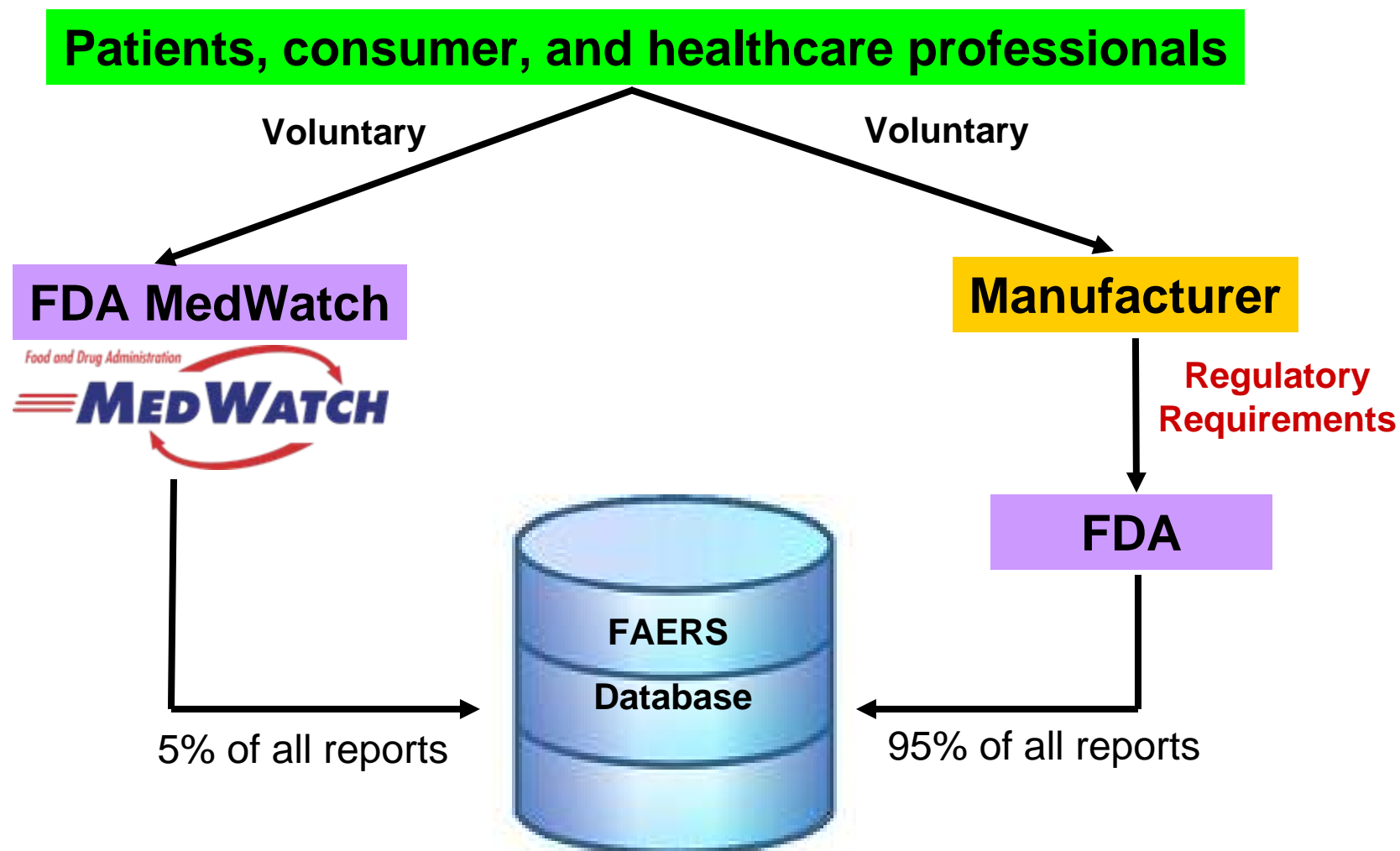
# Postmarket Adverse Event Reporting and MedWatch

## Challenge Question #2

Which of the following countries does not require practitioners to report adverse events to a national registry?

- A. France
- B. Norway
- C. Sweden
- D. US

# How Postmarketing Reports Get to FDA



## Reporting In To MedWatch

1. Patient Identifier
2. Product
3. Event or Problem
4. Reporter

U.S. Department of Health and Human Services

# MEDWATCH

The FDA Safety Information and Adverse Event Reporting System

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page 1 of \_\_\_\_\_

Form Approved OMB No. 0938-0041, Expires: 10/9/2011  
See OMB instruction to users

### I. PATIENT INFORMATION

1. Patient Identifier	2. Age at time of Event or Date of Birth	3. Sex <input type="checkbox"/> Female <input type="checkbox"/> Male
4. Weight _____ lb. or _____ kg.		

(Check all that apply)

5. Adverse Event: ☐ Product Problem (e.g., defective product) ☐ Problem Use Error

6. Outcome Reported to Adverse Event Reporting System (if not report)

☐ Unlabeled Use ☐ Usability or Permanent Damage ☐ Unlabeled Warning ☐ Congenital Anomaly/Birth Defect

☐ Hospitalization - Initial or prolonged ☐ Other Serious (Important Medical Events)

☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

7. Date of Event (month/year) \_\_\_\_\_ 8. Date of this Report (month/year) \_\_\_\_\_

9. Describe Event, Incident or Product of Concern

10. Relevant Terms/History Data, including (if applicable)

11. Other Relevant History, including Pre-existing Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, underlying problems, etc.)

### II. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device <input type="checkbox"/> Health Professional <input type="checkbox"/> Lay User/Patient
Catalog #	Expiration Date (month/year)	<input type="checkbox"/> Other
Serial #	Other #	

6. If Implanted, Give Date (month/year) \_\_\_\_\_ 7. If Implanted, Give Date (month/year) \_\_\_\_\_

8. Is this a Single-use Device that was Reopened and Reused on a Patient?  
☐ Yes ☐ No

9. If Yes to Item 8, Enter Name and Address of Reprocessor

### III. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product Name and Supply Date (include treatment of event)

### IV. REPORTER (See continuously section on back)

Name and Address \_\_\_\_\_  
City \_\_\_\_\_ State \_\_\_\_\_ ZIP \_\_\_\_\_  
Phone # \_\_\_\_\_ Email \_\_\_\_\_

### V. SUSPECT PRODUCT(S)

1. Name, Brand, Manufacturer (from product label)

2. Name: \_\_\_\_\_  
Strength: \_\_\_\_\_  
Manufacturer: \_\_\_\_\_

3. Name: \_\_\_\_\_  
Strength: \_\_\_\_\_  
Manufacturer: \_\_\_\_\_

6. How Reported to: ☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

7. How Reported to: ☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

FORM FDA 3500 (1/99)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.



- How to Report:
  - Online  
([www.fda.gov/medwatch](http://www.fda.gov/medwatch))
  - Download the form
    - Mail
    - Fax 1-800-332-0178
- For questions about the form:
  - 1-800-332-1088

# Spontaneous Reports and FAERS



# Challenge Question #3

## True or False

The actual incidence of adverse drug reactions can never be determined through spontaneous reporting systems.

# Spontaneous Reports

- A communication from an individual (e.g. health care professional, consumer) to a company or regulatory authority
- Describes a suspected adverse event(s)
- Passive and voluntary reports

# Factors Affecting Reporting

- Media attention
- Litigation (class action lawsuits)
- Nature of the adverse event
- Type of drug product and indication
- Length of time on market
- Extent and quality of manufacturer's surveillance system
- Rx or OTC product status
- Reporting regulations

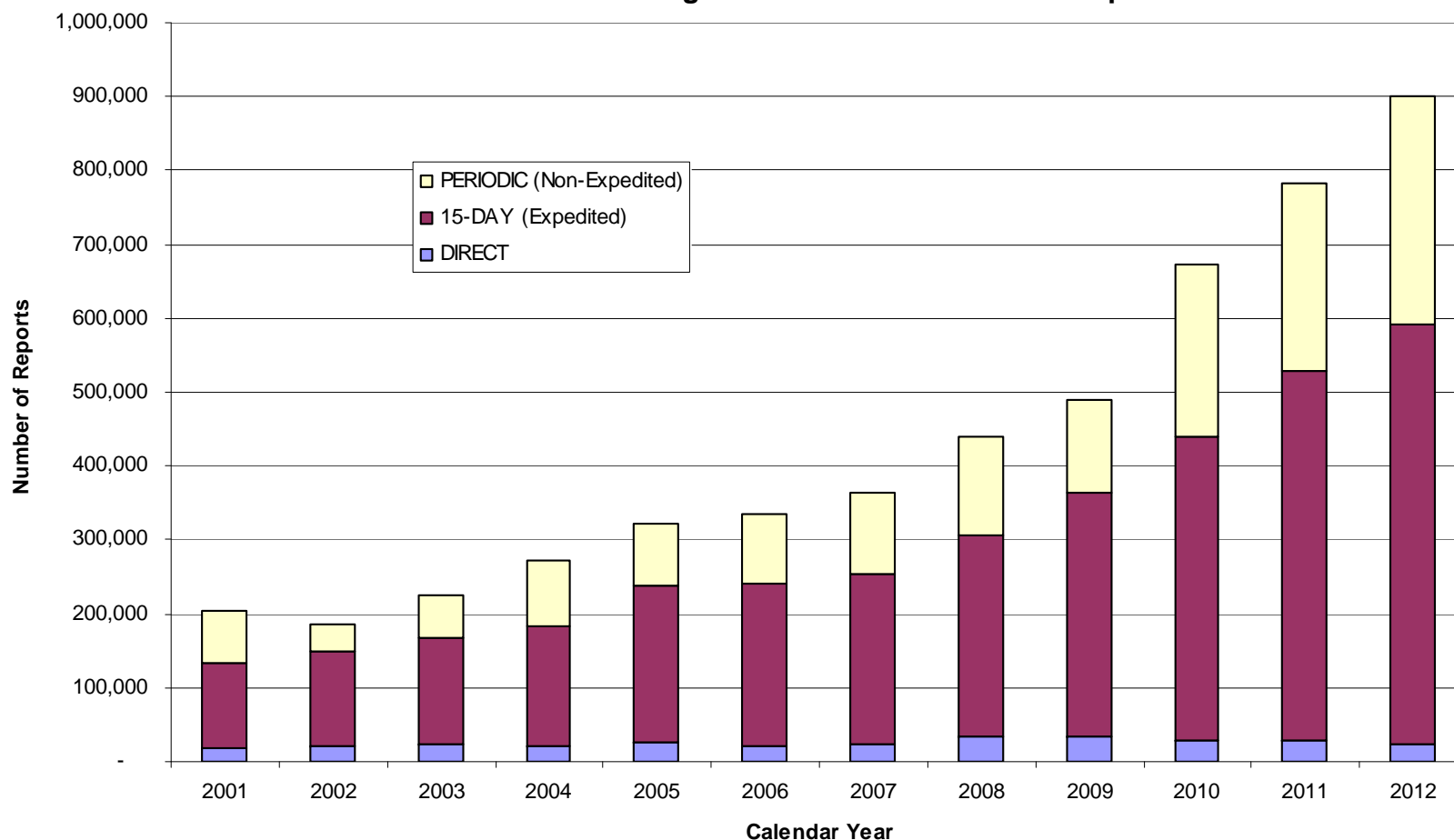
# FDA Adverse Event Reporting System

- Computerized database
- Spontaneous reports
- Contains human drug and therapeutic biologic reports
- > 7 million reports since 1969
- Nearly 1 million new reports in 2012



# Number of Adverse Event Reports Entered into FAERS

**Growing Number of Adverse Event Reports**



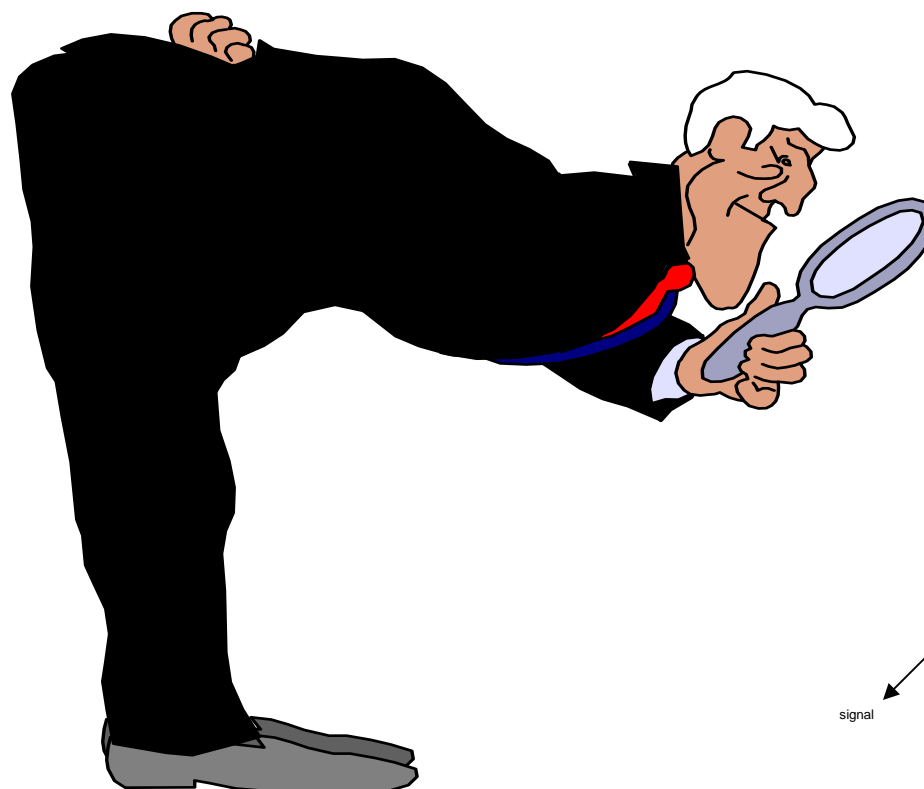
# FAERS Strengths

- Includes all U.S. marketed products
- Includes all uses
- Includes broad patient populations:
  - elderly, children, pregnant women, co-morbidities
- Simple, relatively inexpensive reporting system
- Especially good for events with a rare background rate
- Useful for events that occur shortly after exposure
- Detection of events not seen in clinical trials (“signal generation”)
- Identification of trends, possible risk factors, populations, and other clinically significant emerging safety concerns

# Limitations of FAERS

- Events with high background rates
- Worsening of pre-existing disease
- Issue is beyond the name of the drug
- Comparative incidence rates
- Comparing drugs in the same class
- Disease is reflected in the adverse event
- Looking for drug interactions
- Reporting Biases

# Safety Signal Detection



Did you  
see it??

signal



## Challenge Question #4

**A safety signal is defined as:**

- A. New, previously unknown, adverse event
- B. New drug interaction
- C. An observed increase, either in quantity or severity, of a known adverse event
- D. All of the above

# What is a Safety Signal?

- Reported information on a possible causal relationship between an adverse event and a drug
- The relationship being previously unknown or incompletely documented
- Usually requires more than a single case report to generate a signal
- New unlabeled adverse events
- An observed increase in a labeled event OR a greater severity or specificity
- New interactions
- Newly identified at-risk population



# Sources of Possible Safety Signals

- Routine pharmacovigilance
  - FAERS
  - Datamining
  - Periodic Safety Update Reports
- Study results
- Medical literature
- Media
- New Drug Application (NDA) safety database
- Outside inquiry
- Foreign Regulatory Agencies
- Others



# Use of Data Mining

- Mathematical tool identifies higher-than-expected frequency of product-event combinations
- Tool for hypothesis generation or support for further work on a hypothesis
- Supplements FAERS data review
- Does not replace expert clinical case review



# Case Series Development and Evaluation

# Developing a Case Series

- Use FAERS, published literature, Datamining and other sources to identify safety signal.
- Use knowledge of the clinical course of the disease to perform a thorough database search strategy based on Medical Dictionary for Regulatory Activities (MedDRA) coding

# Principles of Case Evaluation

- Temporal relationship
- Causality assessment- World Health Organization, the Uppsala Monitoring Centre (WHO-UMC):
  - Certain
  - Probable/Likely
  - Possible
  - Unlikely
  - Conditional/Unclassified
- Key factors in causality assessment including, but not limited to
  - Dechallenge/rechallenge
  - Comorbidities
  - Concomitant medications
  - Consistent with pharmacological effects ( biologic plausibility)

# Regulatory Actions

- Labeling changes – i.e. Warnings, Precautions, Adverse Reactions
- Pharmacovigilance activities - enhanced surveillance (e.g., expedited reporting), registry, epidemiology studies
- Risk Evaluation and Mitigation Strategy (REMS)
  - Communication plan, restricted use
- Market withdrawal
- Drug Safety Communication (DSC)

# Communicating Safety Issues

# Communicating Safety Issues to the Public and Internationally

- MedWatch Safety Alerts
- Drug Safety Newsletter
- Postmarket Drug and Biologic Safety Evaluations (FDAAA 915)
- Potential Signals of Serious Risks/New Safety Information Identified from FAERS (FDAAA 921)
- Published literature and scientific meetings
- Video and tele-conferences with foreign regulatory agencies:
  - European Medicines Agency, Canada, Australia, New Zealand

## MedWatch The FDA Safety Information and Adverse Event Reporting Program

Subscribe to MedWatch Safety Alerts

Safety Information

Reporting Serious Problems to FDA

## MedWatch: The FDA Safety Information and Adverse Event Reporting Program

Search MedWatch



Your FDA gateway for clinically important safety information and reporting serious problems with human medical products.

## Spotlight

- 2013 Safety Alerts for Human Medical Products
- Bad Reactions to Cosmetics? Tell FDA!
- Medical Product Safety Educational Resources
- MedWatch Partners

## Resources for You

- Report a Serious Medical Product Problem Online
- Reporting Unlawful Sales of Medical Products on the Internet
- Current Drug Shortages Index
- Index to Drug-Specific Information
- Identifying Recalled Products
- An FDA Guide to Drug Safety Terms

## What's New

- **Samsca (tolvaptan): Drug Warning - Potential Risk of Liver Injury**  
Large clinical trial findings of significant elevations of both ALT and bilirubin. Posted 01/25/2013
- **Bausch and Lomb 27G Sterile Cannula Packed in Amvisc and Amvisc Plus Ophthalmic Viscosurgical Devices (OVD): Class I Recall - Cannulas May Leak or Detach From the Syringe** Some disposable cannulas provided may leak viscoelastic material or detach from the syringe during injection. In rare incidences, detachment has resulted in serious patient injury. Posted 01/23/2013
- **Ferrous Sulfate Tablets, 325 mg Labeled as Rugby Natural Iron Supplement: Recall - Bottle May Contain Meclizine HCl 25 mg Tablets** Serious adverse events may include impaired alertness, drowsiness, confusion, low blood pressure, coma, and respiratory depression. Posted 01/18/2013

[More What's New](#)

## Recalls & Alerts

- MedWatch Safety Alerts for Human Medical Products
- FDA Patient Safety News Video Broadcasts
- FDA Drug Safety Newsletter

## Stay Informed

- Subscribe to MedWatch Safety Alerts
- Join the MedWatch E-list
- About the MedWatch E-list
- Follow MedWatch on Twitter
- MedWatch Safety Alerts RSS Feed
- RSS News Feed Help

## FDA Approved Safety Information

- **DailyMed (National Library of Medicine)**  
Current Drug Prescribing Information. (NOTE: Drugs marked "unapproved" on this site have not been reviewed by FDA for safety and efficacy, and their labeling has not been approved.)
- **Medication Guides**  
Paper handouts that come with many prescription medicines. Medication Guides address issues specific to particular drugs and drug classes. They contain FDA-approved information that can help patients avoid serious adverse events.
- **Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS) (formerly AERS)**
- **Postmarket Drug and Biologic Safety Evaluations**  
Evaluations performed 18 months after drug approval, or after its use by 10,000 individuals.

**<http://www.fda.gov/Safety/MedWatch>**



# Components of a Good Case Report

## Case #1

A nurse reported a male patient started Drug X at 5 mg daily for type 2 diabetes on February 11, 2011. On an unknown date, the patient developed liver failure; additional information was not provided.

## Case #2: Best Case Representative

- 59 yr/ male with history of type 2 diabetes, hyperlipidemia, and hypertension. Patient had no history of liver disease
- Started Drug X on February 11, 2011.
- Other medications include simvastatin and lisinopril.
- Labs drawn on Feb 11 revealed Liver enzymes, INR, Creatinine, and bilirubin normal
- Patient does not drink alcohol
- 8 weeks after starting Drug X patient presented to ER with 5 day history of jaundice, dark urine, and nausea/vomiting
- Admitted to ICU and diagnosed with acute liver failure.
- Drug X stopped upon admission
- All viral hepatitis was ruled out.
- 7 days after stopping medication, all lab values returned to normal.

# Components of a Good Postmarketing Report

- Description of adverse event
- Suspected and concomitant product therapy details (e.g. dose, dates of therapy)
- Patient characteristics (e.g., age, sex), baseline medical condition, co-morbid condition, family history, other risk factors
- Documentation of the diagnosis
- Clinical course and outcomes
- Relevant therapeutic measures and laboratory data
- Dechallenge and rechallenge information
- Reporter contact information
- Any other relevant information

*Guidance for Industry - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005*

# Questions



# References

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<http://www.fda.gov/Safety/MedWatch/SafetyInformation/default.htm>
- MedWatch Safety Alerts: <http://www.fda.gov/Safety/MedWatch/ucm287881.htm>
- MedWatch Safety Alert RSS Feed:  
<http://www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/MedWatch/rss.xml>
- Postmarket Drug Safety Information for Patients and Providers (FDAAA 915):  
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm>
- Postmarketing Drug and Biologic Safety Evaluations: (FDAAA 915):  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm204091.htm>
- Potential Signals of Serious Risks/New Safety Information Identified from AERS (FDAAA 921):  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm#QuarterlyReports>